

PUBLISHED
UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

SIGMA-TAU PHARMACEUTICALS,
INCORPORATED,

Plaintiff-Appellant,

v.

BERNARD A. SCHWETZ, Acting
Principal Deputy Commissioner,
Food and Drugs; TOMMY G.
THOMPSON, Secretary, Department of
Health and Human Services,

Defendants-Appellees,

and

GENSIA SICOR PHARMACEUTICALS,
INCORPORATED,

Intervenor-Appellee.

No. 01-2206

Appeal from the United States District Court
for the District of Maryland, at Greenbelt.
Catherine C. Blake, District Judge.
(CA-01-1377-CCB)

Argued: April 3, 2002

Decided: May 2, 2002

Before WILKINSON, Chief Judge, WIDENER, Circuit Judge,
and Walter K. STAPLETON, Senior Circuit Judge of the
United States Court of Appeals for the Third Circuit,
sitting by designation.

Affirmed by published opinion. Chief Judge Wilkinson wrote the
opinion, in which Judge Widener and Senior Judge Stapleton joined.

COUNSEL

ARGUED: Mark D. Gately, HOGAN & HARTSON, L.L.P., Baltimore, Maryland, for Appellant. Barbara Jeanne Stradling, Office of Consumer Litigation, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C., for Federal Appellees; David G. Adams, VENABLE, BAETJER, HOWARD & CIVILETTI, L.L.P., Washington, D.C., for Appellee Gensia Sicor. **ON BRIEF:** Steven F. Barley, HOGAN & HARTSON, L.L.P., Baltimore, Maryland; Catherine E. Stetson, HOGAN & HARTSON, L.L.P., Washington, D.C., for Appellant. Robert D. McCallum, Jr., Assistant Attorney General, Larry D. Adams, Assistant United States Attorney, Office of Consumer Litigation, UNITED STATES DEPARTMENT OF JUSTICE, Washington, D.C.; Daniel E. Troy, Chief Counsel, Carl I. Turner, Associate Chief Counsel, UNITED STATES FOOD AND DRUG ADMINISTRATION, Washington, D.C., for Federal Appellees.

OPINION

WILKINSON, Chief Judge:

Sigma-Tau Pharmaceuticals, Inc. claims that the Food and Drug Administration acted contrary to law in approving generic versions of its levocarnitine drug because the generics infringed on the seven-year period of orphan exclusivity that its drug currently enjoys under the Orphan Drug Act, 21 U.S.C. §§ 360aa-ee. The district court disagreed, concluding that the FDA did not act unlawfully in approving the generics for an indication that was no longer protected by market exclusivity under the Act. Because the district court correctly interpreted the governing statute's clear language, we affirm.

I.

Sigma-Tau Pharmaceuticals developed a drug to treat a rare condition known as carnitine deficiency in people with inborn metabolic disorders.¹ The FDA designated Sigma-Tau's levocarnitine drug an

¹Carnitine is a naturally occurring amino acid derivative produced by the liver and kidneys and found in red meat and dairy products. It trans-

"orphan drug" — one designed to treat a rare disease or condition — and approved Sigma-Tau's application to market it. Under the Orphan Drug Act ("ODA"), 21 U.S.C. §§ 360aa-ee, Sigma-Tau was entitled to seven years of market exclusivity to sell its drug, known as Carnitor, for that orphan indication. Its exclusivity for inborn metabolic disorders expired in 1999.

Sigma-Tau later received FDA approval for use of its levocarnitine drug for the prevention and treatment of a second rare condition — carnitine deficiency in patients with end-stage renal disease ("ESRD") who are undergoing dialysis. Sigma-Tau's exclusivity for treating carnitine deficiency in ESRD patients expires in 2006.

The FDA recently approved the applications of two drug manufacturers, private intervenor Gensia Sicor Pharmaceuticals, Inc. and Bedford Laboratories, to market and sell generic forms of Sigma-Tau's levocarnitine drug. The agency approved the generics for the treatment of patients with inborn metabolic disorders, the unprotected indication. The generics compete with Carnitor.

As a result of these generic drug approvals, Sigma-Tau brought suit against the FDA on May 10, 2001. Sigma-Tau sought to have the approvals rescinded, or, in the alternative, to have the FDA change the generics' labeling to protect Sigma-Tau's orphan exclusivity. Sigma-Tau claimed that the FDA had violated the ODA Amendments to the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 360aa-ee, the ODA's implementing regulations, and the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A). In particular, Sigma-Tau alleged that the FDA ignored substantial evidence that the generics were intended for use in an orphan-protected market, and that the agency's approvals were arbitrary and capricious because the generics infringed on the seven-year period of orphan exclusivity that Carnitor currently enjoys under the ODA.

ports long-chain fatty acids into the mitochondria, where they are oxidized and release energy. It also functions as a waste remover. Carnitine deficiency can manifest itself in many ways, including the failure to thrive in infants, cardiomyopathy, recurrent infections, muscle weakness, and liver dysfunction.

After two hearings, the district court ruled against Sigma-Tau. In so ruling, the district court applied the well-settled principles of *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Under the first step of the *Chevron* analysis, *id.* at 842-43, the court concluded that Congress had spoken directly to the issue, and that the FDA's approvals of the generic manufacturers' products were consistent with the clear language of the governing statute, § 360cc(a) of the ODA. Noting the statute's directive that the FDA "may not approve another application . . . for such drug for such disease or condition . . . until the expiration of seven years," *id.*, the court reasoned that the FDA had not approved another drug application "for such disease or condition," but rather had done so for a disease or condition no longer subject to exclusivity.

Alternatively, the court held that even if the statute was not clear, the FDA's permissible construction of it was entitled to deference under the second step of the *Chevron* inquiry. *See* 467 U.S. at 843-44. Further, the court concluded that the agency was entitled to substantial deference in interpreting its own regulations, especially on a complex and highly technical issue.

The court thus held that the FDA's approvals were "not arbitrary or capricious, an abuse of discretion, or otherwise a violation of law." It accordingly entered judgment in favor of the agency. Sigma-Tau appeals.

II.

In dispute here are provisions of the FDCA that govern orphan drugs. *See* 21 U.S.C. §§ 360aa-360ee. These sections were added to the FDCA by the Orphan Drug Act of 1983 ("ODA"), Pub. L. No. 97-414, 96 Stat. 2049. The ODA was enacted in order to provide drug manufacturers with incentives to develop "orphan" drugs — that is, drugs for the treatment of rare diseases or disorders that affect only small patient populations. *See Genentech, Inc. v. Bowen*, 676 F. Supp. 301, 302-303 (D.D.C. 1987). In pursuit of this objective, Congress offered research assistance, grants, and tax incentives to companies that undertake development of orphan drugs. *Id.* at 303. In addition, Congress provided for seven years of market exclusivity for approved orphan drugs. 21 U.S.C. § 360cc(a). As noted above, this provision of

the ODA states that the FDA "may not approve another application . . . for such drug for such disease or condition . . . until the expiration of seven years." *Id.*

Sigma-Tau challenges the FDA's approvals of generic versions of Carnitor. Sigma-Tau submits that the generics were in fact intended for use in patients with ESRD who are undergoing dialysis, and that they thereby infringed on the seven-year period of orphan exclusivity that Carnitor currently enjoys under the ODA.

III.

A.

Reviewing the district court's grant of summary judgment *de novo*, see *Higgins v. E.I. DuPont de Nemours & Co.*, 863 F.2d 1162, 1167 (4th Cir. 1988), we agree that the plain language of the ODA is unambiguous, and that the FDA's approvals of the generics in this case comported with the clear wording of the statute. It is apparent that the FDA did not "approve another application . . . for such drug for such disease or condition" here, § 360cc(a), but rather approved "another application . . . for such drug" for a different disease or condition, one that was no longer subject to exclusivity. That is, the agency approved generic versions of Sigma-Tau's levocarnitine drug for people with inborn metabolic disorders, for which the period of orphan exclusivity had expired. The FDA did not approve the generics for the treatment of ESRD patients.

By using the words "such drug for such disease or condition," Congress made clear its intention that § 360cc(a) was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses. Congress could have written § 360cc(a) more broadly by prescribing that the FDA "may not approve another application . . . for such drug," but it chose not to draft the statute in that way. Because Congress has spoken directly to the dispositive question before us, our inquiry is at an end. *Chevron*, 467 U.S. at 842-43; see also *Hillman v. IRS*, 263 F.3d 338, 342 (4th Cir. 2001) (citing *Caminetti v. United States*, 242 U.S. 470, 485 (1917)).

Understanding the implications of this analysis under the first step of *Chevron*, Sigma-Tau argues that the plain language of § 360cc(a) is ambiguous. Specifically, Sigma-Tau submits that the phrase "such disease or condition" may refer either to the disease or condition for which the drug is labeled, or to the disease or condition for which it is intended to be used.

But Sigma-Tau cannot create a genuine ambiguity in § 360cc(a) under *Chevron* by raising the evidentiary question of labeled use versus intended use. Section 360cc(a) simply provides that the FDA "may not approve" generics for a protected indication. Thus, the statute is clearly directed at FDA approved-use, not generic competitor intended-use. And in view of this textual emphasis on approved-use, the evidentiary basis for the agency's approvals must be the use for which the approvals are sought — that is, the use for which the generics are labeled. Thus, the FDA does not violate § 360cc(a) by relying upon the generic manufacturers' proposed labeling as opposed to the alleged evidence of intended use discussed below. This statute is not ambiguous.

B.

Sigma-Tau nevertheless urges us to look beyond the face of the ODA to the FDA's regulations. In particular, Sigma-Tau contends that if the agency had properly applied its intended-use regulation, 21 C.F.R. § 201.128 (2001), it would have concluded that the generics at issue were intended for treatment of ESRD patients. Sigma-Tau asserts that the FDA should have considered "compelling, readily available, objective evidence of the generics' intended use," such as market data for Carnitor, dosage forms, and federal drug reimbursement policies, which would have resulted in the generics not being approved based on 21 C.F.R. § 316.3(b)(13) (2001).²

²Specifically, Sigma-Tau claims: (1) data show that 80% of the market for Carnitor is for treating ESRD; (2) Gensia Sicor and Bedford Labs sought approval only for the injectable form of the drug, which is the only form approved for treating ESRD; and (3) the Centers for Medicare and Medicaid Services, the federal agency reimbursing 93% of ESRD treatments in the United States, does not distinguish between orphan and generic drugs in making payments.

To reiterate, the statute has foreclosed this line of argument. And even if we were to consider the regulations, application of § 201.128 does not entitle Sigma-Tau to relief. Sigma-Tau does not attack the validity of the FDA regulations themselves. Because Sigma-Tau raises no challenge to the validity of the regulations themselves, we have no occasion to consider the deference due the FDA's interpretation of the ODA under *United States v. Mead Corp.*, 533 U.S. 218 (2001). *Mead* accords *Chevron* deference to agency interpretations that take the form of rules promulgated pursuant to an express grant of "authority to the agency generally to make rules carrying the force of law." *Id.* at 226-27.

Rather, Sigma-Tau challenges the agency's application of the regulations to the facts of this case. We owe "substantial deference" when reviewing an agency's interpretation of its own regulations. *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see also Zeneca, Inc. v. Shalala*, 213 F.3d 161, 168 (4th Cir. 2000); *Friends of Iwo Jima v. Nat'l Capital Planning Comm'n*, 176 F.3d 768, 775 (4th Cir. 1999). We must defer to the FDA's interpretation of its regulations unless it is "plainly erroneous or inconsistent with the regulation." *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (internal quotations omitted); *see also Thomas Jefferson Univ.*, 512 U.S. at 512; *Zeneca*, 213 F.3d at 168. Indeed, "[o]ur review in such cases is more deferential than that afforded under *Chevron*." *Wyo. Outdoor Council v. U.S. Forest Serv.*, 165 F.3d 43, 52 (D.C. Cir. 1999) (internal quotation omitted). The "broad deference" due the agency "is all the more warranted when, as here, the regulation concerns 'a complex and highly technical regulatory program,' in which the identification and classification of relevant 'criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.'" *Thomas Jefferson Univ.*, 512 U.S. at 512 (quoting *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991)).

The FDA's application of its regulations to the facts before it was not erroneous. On the contrary, the agency's approvals of the generics were reasonable in view of the language of the regulations implementing the orphan drug provisions of the FDCA. They state that "[o]rphan-drug exclusive approval . . . means that . . . no approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years" 21 C.F.R. § 316.3(b)(12) (2001).

"Same drug" is defined as "a drug that . . . is intended for the same use as the previously approved drug." 21 C.F.R. § 316.3(b)(13)(i). And "intended use" is defined as "the objective intent of the persons legally responsible for the labeling of drugs." 21 C.F.R. § 201.128. Section 201.128 further provides that "intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article."

The FDA determined the intended use for Gensia Sicor's and Bedford Labs' generic drugs by relying primarily upon the proposed labeling provided by the companies. In so doing, the FDA did not contravene § 201.128. The manufacturers' labels certainly constitute "such persons' expressions" within the meaning of that section. Indeed, § 201.128 specifically mentions "labeling claims" and "written statements" by manufacturers. As we have previously affirmed, "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FDCA] absent manufacturer claims as to that product's use." *Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation omitted), *aff'd*, 529 U.S. 120 (2000).

Sigma-Tau contends that the FDA was obligated to look beyond the labeling to what Sigma-Tau maintains is the reality of the situation, which is that most of the need for the generics — and thus most of the money to be made — lies in treating patients with ESRD. But this point is unavailing. Section 201.128 provides that "intent is determined by such persons' expressions *or may be shown* by the circumstances surrounding the distribution of the article" (emphasis added). The regulation is phrased in the disjunctive, not the conjunctive. And it states that intent "may be shown" by the surrounding circumstances, not that it must be so shown. The district court correctly found that § 201.128 grants the agency discretion to decide what evidence of intent it will examine.

The regulation does so for good reason. The FDA necessarily approves the generics before their manufacturers engage in any actual marketing. This is obvious enough, but the potential consequences of following Sigma-Tau's approach in view of this fact may not be. If we were to ignore the deference due the FDA and impose exacting evidentiary standards upon its generic drug approval process, the

agency would be faced with formidable problems. This is because many of the sources of evidence and market data to which Sigma-Tau points cannot be effectively analyzed in the pre-approval context. As the FDA stresses, that is why § 201.128 provides the agency with flexibility, and why it states that "[t]he intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer." Thus, the intended-use inquiry Sigma-Tau urges upon us might evolve into a foreseeable-use test. Then, once the FDA approved an orphan drug for a protected indication, generic competitors might be prohibited from entering the market for almost any use.

As the district court noted, not only might this course of events result in extensions of exclusivity periods that Congress never intended, but it also might frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses. *See, e.g., Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1496 (D.C. Cir. 1996); *Rhone-Poulenc Rorer Pharm., Inc. v. Marion Merrell Dow, Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996). In light of the ensuing effects on the delivery of health care and drug prices in this country, such interference with off-label use is not something we would be wise to welcome, let alone help to bring about. Even Sigma-Tau appears to agree that the medical community's foreseeable off-label use of drugs does not violate the ODA.

In arguing that the FDA cannot accept the generic competitors' representations but rather must draw inferences from market forces, Sigma-Tau is in effect campaigning for a regulatory regime in which relatively few generics are approved. Though it does not couch its contentions in these terms, Sigma-Tau in essence wants foreseeable off-label use to bar the approval of generic drugs, even for unprotected indications. But the consequences of adding a huge evidentiary hurdle to the generic drug approval process would be profoundly anti-competitive. And that is not all. Sigma-Tau's approach also implicitly frowns upon the practice of off-label use itself. But the Supreme Court has not indicated that off-label use is illegitimate. On the contrary, it recently stated that "'off-label' usage of medical devices . . . is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medi-

cine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).

In addition, the FDA persuasively argues that it must balance the ODA's incentive structure for the development of orphan drugs against the goals of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Amendments to the FDCA. Pub. L. No. 98-417, 98 Stat. 1585. This statute seeks "to make available more low cost generic drugs" by establishing an abbreviated generic drug approval procedure. H.R. Rep. No. 98-857(I), at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647. Rather than balancing the ODA and the Hatch-Waxman Amendments, Sigma-Tau quite unapologetically puts all weight on the orphan drug development end of the scale, as if no tension exists between the two statutes that the FDA must negotiate.

Thus, the FDA did not commit plain error or act inconsistently with its regulations insofar as it declined to examine other evidence besides the proposed labeling in approving the generic drugs at issue. *See Auer*, 519 U.S. at 461. Accordingly, the agency's approvals were not "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).³

³Sigma-Tau contends that the FDA's generic approvals also violated the "same labeling" requirement of the FDCA, which mandates that the labeling of a generic drug be exactly the same as that of the innovator, except for certain specified differences. 21 U.S.C. § 355(j)(2)(A)(v). But as the FDA correctly points out, one of the permissible discrepancies concerns labeling "changes required . . . because the new [generic] drug and the listed drug are produced or distributed by different manufacturers." *Id.* Given that the generics in this case are not allowed to have the same labeling as Carnitor while Carnitor is enjoying a second seven-year period of exclusivity for the treatment of ESRD, Sigma-Tau's argument constitutes nothing more than another attempt to obtain market exclusivity for any and all uses of its drug, thereby preventing generic competitors from entering the market for any indication. Indeed, the D.C. Circuit rejected Sigma-Tau's proposed interpretation of 21 U.S.C. § 355(j)(2)(A)(v) for primarily this reason in the context of Hatch-Waxman pioneer-drug exclusivity under 21 U.S.C. § 355(j). *See Bristol-Myers*, 91 F.3d at 1499-1500.

IV.

The statute governing the outcome of this case is clear on its face. And even if it were not, the FDA's application of its regulations here was not in error. If the underlying facts of this dispute are as Sigma-Tau alleges — that the generic manufacturers said one thing to the agency when they intended to do something else from the very start — then the FDA may reconsider its approvals of their generics at a later date. But the FDA is not obligated to assume bad faith on the part of generic manufacturers at the beginning of the approval process. And neither the controlling statute nor FDA regulations require the agency to do more than it did in this case. For the foregoing reasons, the judgment of the district court is

AFFIRMED.